REMARKS

Claims 1-19, 30-31 and 42-56 are cancelled; these claims are cancelled to expedite prosecution and applicant reserves the right to present these claims in a continuation application. Claims 20-29, 32-41 and 57-74 are pending. Upon entry of this amendment, claims 21-29, 32-37, 39-42 and 57-74 are amended.

I. Priority

The Examiner asserts that the parent applications do not support the instant method of use.[1] Applicant respectfully submits that the methods of use are supported by at least one parent application. Generally, the claimed methods of use are directed to preventing or treating ototoxicity in a patient exposed to noise for a time and at an intensity sufficient to result in ototoxicity by administration of an otoprotective agent comprising methionine. U.S. Application Serial No. 09/057,065 (now U.S. Patent No. 6,265,386) was filed on April 8, 1998 and the specification supports the claimed methods of use. For example, the specification discloses "the present invention provides a method for preventing or reducing ototoxicity in a patient exposed to noise for a time and at an intensity sufficient to result in ototoxicity, comprising administering to the patient an anti-ototoxic effective amount of a methionine protective agent."[2] There are similar passages throughout the specification as well as a section describing noise-induced hearing loss in the specification.[3] After the description of methionine protective agents of the invention, the specification discloses "these methionine protective agents can be employed ... in methods for treating human and animal patients exposed to ototoxic noise levels...."[4] Accordingly, the claimed methods of use

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[1]See Office action dated August 23, 2004 at page 2.

[2]Column 5, lines 63-67 of U.S. Patent No. 6,265,386.

[3]Column 17, line 45 - column 18, line 4 of U.S. Patent No. 6,265,386.

[4]See page , column 18, line 62 - column 19, line 2 of U.S. Patent No. 6,265,386.

are supported by the specification of U.S. Application Serial No. 09/057,065 and thus, have a priority date of April 8, 1998.

II. Campbell Declaration

The Examiner states that the Declaration of June 15, 2004 by Dr. Campbell would not be persuasive, even if signed, because it is opinion only. Applicant respectfully requests reconsideration of the Campbell declaration simultaneously submitted herewith, as it is signed and contains underlying facts, which are probative. The Campbell declaration has been modified and amplified since the version dated June 15, 2004 was submitted. Although opinion on the ultimate legal conclusion is not probative, a persuasively supported statement by a person skilled in the art about what was not obvious is probative.[5] In this case, Dr. Campbell has stated that her invention was not obvious from the Campbell et al. reference based on her knowledge of the art combined with reasonable inferences a person skilled in the art would have made upon review of the reference. The statements directed to the knowledge of a person skilled in the art and reasonable inferences derived from the reference support her conclusion that her invention as defined by the subject claims was not obvious, and thus, her signed declaration must be regarded as probative. It is respectfully submitted that, in reaching an ultimate evaluation of obviousness *vel non*, the Examiner must give proper weight both to the opinions expressed by Dr. Campbell and the factual analysis by which those opinions are supported.

III. 35 U.S.C. § 112 Rejections

Reconsideration is respectfully requested of the rejection of claims 3-4, 15, 21-29 and 32-74 under 35 U.S.C. § 112, second paragraph, as indefinite.

Claims 1, 3-4, 15, and 42-56 are cancelled, thus the rejection is moot with respect to these claims.

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[5]See In re Lindell, 385 F.2d 453 (CCPA 1965).

Claims 57 and 71 are amended to state "provided that, at the same time said otoprotective agent is administered, an antineoplastic effective dose of cisplatin has not been administered or prescribed for administration to said patient." The words "administered or" were added to make it clear that the patient has not received and is not receiving cisplatin.

Claims 21-29, 32-37, 39-41, 58-70 and 72-74 are amended as suggested to make their dependent status clear. In view of these amendments, it is respectfully requested that the rejections under 35 U.S.C. § 112 be withdrawn.

IV. 35 U.S.C. § 102 and § 103 Rejections over Campbell et al.

Applicant respectfully submits that Campbell et al., Hearing Research 102 (1996) 90-98, does not inherently anticipate claims 20-29 and 32-41. Campbell et al. disclose the treatment of five groups of rats. These groups were an untreated control, a treated control (16 mg/kg cisplatin), and three treated experimental groups ((1) 75 mg/kg D-methionine + 16 mg/kg cisplatin; (2) 150 mg/kg D-methionine + 16 mg/kg cisplatin; and (3) 300 mg/kg D-methionine + 16 mg/kg cisplatin). Campbell et al. do not address any other cause of ototoxicity except that from cisplatin. In addition, D-methionine was not used to treat human patients; rats were the experimental subjects.

The Office has asserted that there would inherently be a subset of those patients exposed to cisplatin as described in Campbell et al., that were also exposed to ototoxicity-inducing noise. However, inherency may not be established if there is only a probability or possibility that a certain result may occur.[6] There is no disclosure by Campbell et al. that shows that any of the rats in any of the five groups were exposed to a level of noise that would cause ototoxicity. Even if it were possible that a subset of the rats were also exposed to an ototoxic level of noise, there is nothing in the disclosure in Campbell et al. from which it can be shown that such exposure inevitably did occur. Moreover, the Campbell declaration states that the rats were in a controlled environment during testing and purposefully not exposed to an ototoxic level of noise.

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[6] *In re Oelrich*, 666 F.2d 578.

Accordingly, Campbell et al. do not disclose any facts which would support even a possibility that any subset of rats were actually exposed to both an ototoxic level of cisplatin and an ototoxic level of noise. Because the Campbell declaration affirmatively states that care was taken to avoid exposing the rats tested to an ototoxic level of noise, there is essentially zero likelihood that they were so exposed. Thus, claims 20-29 and 32-41 are not anticipated by Campbell et al.

Because Campbell does not teach the administration of methionine or any other compound for treatment of noise-induced ototoxicity and contains no inherent disclosure of such treatment, either incidental to treatment of cisplatin-induced hearing loss or otherwise, there is no basis for the §103 rejection of claims 20-29 and 32-41 over Campbell. The Examiner's conclusion that it would have been obvious to treat noise-induced otoxicity with L-methionine is based on the premise that Campbell inherently treats noise-induced hearing loss with D-methionine. But the premise is erroneous. As there is no basis remaining for the §103 rejection over Campbell, it is respectfully requested that this ground of rejection be withdrawn.

V. 35 U.S.C. § 102 and § 103 Rejections over Kopke et al.

As detailed above, the priority date of the subject claims is April 8, 1998, so only the Kopke provisional application (U.S. application serial no. 60/069,761) filed on December 16, 1997 is prior to the priority date of the subject claims. Accordingly, only the disclosure of the Kopke provisional is discussed.

A. Novelty

Claims 20-29, 32-41 and 57-74 are directed to methods for preventing or treating ototoxicity in a patient exposed to noise by administering an effective amount of an otoprotective agent comprising methionine. It is respectfully submitted that Kopke contains no specific teaching of the administration of methionine for treatment of hearing loss, and particularly fails to teach or suggest the unique advantages of methionine for such purpose. In this connection, it should be recognized that Kopke's

provisional disclosure is not limited to treatment of noise-induced hearing loss, but instead relates to hearing loss from a variety of disparate insults including aminoglycoside antibiotics, chemotherapeutic agents, noise, and closed head injuries. Kopke discloses that applying R-N6-phenylisopropyl adenosine (R-PIA) to the round window membrane of the inner ear or systemically is effective to combat hearing loss by upregulating the activity of γ-glutamyl cysteine synthase for intracellular synthesis of glutathione. Kopke further discloses the optional administration of a sulfur compound to serve as substrate for glutathione synthesis. Methionine is mentioned along with a number of other sulfur compounds, prominently oxothiazolidine-4-carboxylic acid (OTC), that can be transported into an inner ear hair cell and serve as a substrate for glutathione synthesis.

However, Kopke does not suggest that methionine is specific for treatment of noise-induced hearing loss, as opposed to hearing loss resulting from chemotherapeutic agents, aminoglycoside antibiotics, or closed head injuries. Moreover, there is no emphasis in the Kopke reference on the administration of any particular sulfur compound other than OTC; and the principal teaching is the administration of R-PIA for upregulating antioxidant enzymes such as γ-glutamyl cysteine synthase, and upregulating adenosine in neural tissue to decrease the release of potentially damaging excitotoxic amino acids such as glutamate and thereby limit NO damage.

With respect to the specific problem of noise-induced hearing loss, nothing in Kopke would lead a person skilled in the art to select methionine over other compounds that could be transported into an inner ear hair cell and synthesized into glutathione or to select methionine over the other compounds disclosed (e.g., L-2-oxothiazolidine-4-carboxylic acid (OTC), L-N-acetylcysteine (L-NAC), S-adenosyl-L-methionine (SAMe)). Moreover, Kopke et al. effectively teach away from selection of methionine. For example, Kopke et al. primarily discuss OTC (also called procysteine) as the compound that can be transported into an inner ear hair cell and synthesized into glutathione. In addition, the examples (Figures 1 and 2) disclose use of the adenosine agonist, R-PIA,

by itself as a compound which reduces hearing loss from a noise insult. Accordingly, in the specific case of noise-induced hearing loss, Kopke et al. would not have led a person skilled in the art to select methionine from the possible compounds that can be transported into an inner ear hair cell and synthesized into glutathione, and thus, the subject claims are not anticipated by the Kopke provisional application.

B. Nonobviousness

Claims 20-29, 32-41 and 57-74 would not have been rendered obvious by the Kopke provisional application. Since the reference treats the administration of a sulfur compound as merely optional, and contains no guidance for the selection of any specific sulfur compound to promote glutathione synthesis in the treatment of noise-induced hearing loss, it is respectfully submitted that the claimed method calling for the administration of methionine is not rendered *prima facie* obvious by Kopke. Moreover, *prima facie* obviousness must be evaluated against the entire background of the art, not just against an isolated reference which can be selected by searching with the inventor's claims at hand.[7] As detailed in the accompanying declaration of Dr. Campbell, it is known that the mechanisms causing hearing loss differ markedly among the various insults from which hearing loss results, that the effectiveness against any particular cause of hearing loss varies among sulfur compounds, and that the effectiveness of any particular sulfur compound typically varies among the causes of hearing loss. Thus, absent more specific teaching by Kopke, one skilled in the art would not have been led to expect that all of the sulfur compounds listed would be effective against all sources of hearing loss, or that methionine in particular would be effective against hearing loss as arising specifically from exposure to noise.

Even if *prima facie* obviousness could otherwise be established, it is respectfully submitted that any such finding should be overcome by the empirical evidence presented in the attached Campbell declaration. The data presented and described by Dr. Campbell demonstrate that D-methionine alone, without the co-administration of R-

[7] *In re Kuderna*, 165 U.S.P.Q. 575 (C.C.P.A. 1970).

PIA, has a decidedly beneficial effect against noise-induced hearing loss. As further explained in the declaration, this beneficial effect is believed to result, at least in part, from the function of methionine as an antioxidant, and not merely as a substrate for the γ-glutamyl cysteine synthase catalyzed intracellular synthesis of glutathione as described by Kopke. For example, attached data show the ratio of reduced glutathione (GSH) to oxidized glutathione (GSSG) is increased by administration of D-methionine. The effect of D-methionine on the GSH/GSSG ratio may be more important than the absolute glutathione concentration to protection of a subject from noise-induced hearing loss. Even for glutathione synthesis, Kopke emphasizes the importance of upregulating the synthase by administration of an adenosine agonist such as R-PIA, apparently to accelerate the rate of glutathione formation and/or to increase glutathione to supranormal levels. Applicant has found that methionine is effective without the necessity of administering an adenosine agonist. The striking result achieved by D-methionine, which is not predicted by Kopke or other references known to applicant, constitutes substantial secondary evidence overcoming any *prima facie* obviousness which the Kopke disclosure might otherwise be deemed to create.[8]

It is recognized that the data presented in the Campbell declaration relate specifically only to D-methionine. However, as Dr. Campbell testifies, it is now reasonable to expect that they should at least establish useful efficacy for the racemic mixture which includes 50% of the D-isomer. Although the efficacy of the L-isomer has not been demonstrated empirically, it is Dr. Campbell's further expectation that it will also be effective, irrespective of the presence or absence of an adenosine agonist such as R-PIA, especially in view of the apparent ability of methionine to be reversibly oxidized and to function as a direct free radical scavenger. See Campbell declaration,

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[8] Where present, secondary evidence must be considered in evaluating obviousness; *Demaco Corporation v. F. von Langsdorff Licensing Limited*, 851 F.2d 1387, 7 USPQ2d 1222 (Fed. Cir. 1988). "Indeed, evidence of secondary considerations may often be the most probative and cogent evidence in the record;" *Stratoflex v. Aeroquip*, 713 F.2d 1530, 1538-1539, 218 USPQ 871 (Fed. Cir. 1983)

paragraph 20.[9] Thus, it is respectfully submitted that any basis for *prima facie* obviousness has been overcome, and that claims 20-29, 32-41 and 57-74 should be deemed patentable over Kopke under 35 U.S.C. §103.

When weighing rebuttal evidence, the Office should avoid giving it no weight.[10] The specific and strikingly beneficial effect of methionine against noise-induced ototoxicity would not have been obvious from a reference which attempts to deal with multiple causes of hearing loss, and which indiscriminately lists methionine with a number of other sulfur compounds without describing which of these compounds would be effective which causes of ototoxicity. The determination of patentability should be made on the entire record where the facts of rebuttal are considered along with the facts establishing the *prima facie* case of obviousness. Stated another way, competent rebuttal evidence requires the Office to start the nonobviousness analysis again by evaluating all the evidence–facts supporting and facts rebutting the *prima facie* case–and determining whether, on the whole record, the invention is nonobvious.[11]

In a series of studies undertaken, D-methionine was tested for protection and rescue of animals exposed to noise. These studies were conducted at the direction of applicant, Dr. Campbell, and the results are presented in the Campbell declaration. The results show that D-methionine administration to the animals significantly decreased the threshold shift, significantly decreased the outer hair cell (OHC) and inner hair cell (IHC) loss and significantly increased the ratio of reduced glutathione (GSH) to oxidized glutathione (GSSG) in the cochlea as compared with the control animals. Additionally, although the number of animals tested for the rescue effect of D-methionine was not sufficient for a rigorous statistical analysis, the trend in the ABR

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[9] If the Examiner deems it necessary, applicant is prepared to obtain and provide data on the efficacy of L-methionine vs. noise-induced hearing loss. However, Kopke discloses only "methionine" without specific connection to noise induced hearing loss; so it is believed that the noise data for D-Met should suffice for patentability of claim 20. At all events, the data submitted should be sufficient to support patentability of claims 22 and 59 which specifically require D-methionine.

[10] See MPEP 2144.08.

[11] See MPEP 706.01.

threshold data 21 days after noise exposure showed a smaller threshold change in the D-methionine treated groups as compared to the treated control group. Thus, the data presented in the Campbell declaration were striking in view of the Kopke et al. disclosure emphasizing the importance of an agent (e.g., R-PIA) which upregulates an antioxidant enzyme activity for treating the effect of various insults on hearing.

Furthermore, Kopke et al. do not enable a person of ordinary skill to use the whole range of compounds for all ototoxic insults as disclosed. This deficiency is apparent from the variation in causative mechanisms of hearing loss, differences in efficacy among various sulfur compounds in treating hearing loss, and differences in therapeutic mechanisms of different sulfur compounds, all as alluded to above, detailed in the Campbell declaration, and discussed generally hereinbelow. If the Kopke article is read in light of these real world considerations, it cannot be construed as teaching that each of the listed sulfur compounds is effective against hearing loss caused by each of the listed insults; or, if the Kopke reference is so construed, it must be deemed non-enabling. For example, one skilled in the art should not interpret Kopke et al. as categorically teaching that all compounds that can be transported into an inner ear hair cell and synthesized into glutathione are effective against hearing loss due to administration of aminoglycoside antibiotics, chemotherapeutic agents, noise exposure and closed head injuries. For in the Campbell declaration, Dr. Campbell presents evidence that it is uncertain whether all compounds that can be transported into an inner ear hair cell and synthesized into glutathione are effective against hearing loss arising from each of the disclosed insults because mechanisms of hearing loss differ among insults, therapeutic mechanisms differ among insults, and the effectiveness of similar compounds for a given insult differs greatly.

Moreover, as described in more detail in the Campbell declaration, the morphology, physiology and biochemistry of the cells of the ear differ among causes. For example, noise causes temporary vasoconstriction in the auditory system and noise-induced hearing loss may be secondary to reperfusion injury. In addition, noise can induce microlesions in cochlear hair cell plasma membranes, breaks in the reticular

lamina, and glutamate excitotoxicity at the synapse of the spiral ganglion. Furthermore, noise exposure induces expression of heat shock proteins in the cochlea and changes cochlear gene expression. In contrast, cisplatin does not induce the above cell changes. Cisplatin can damage cells by causing DNA intra- and interstrand cross links preventing cell replication and by binding to the L-methionine in protein and disrupting the protein and damaging or killing cells. Additionally, cisplatin may soften the cuticular plate and cause more lysosomal bodies to be present in the OHC's apical portion. Furthermore, cisplatin can cause strial changes of cystic degeneration and protrusions into the endolymphatic duct prior to cell death.

Additionally, although there may be some common therapeutic mechanisms for plural causes, many therapeutic mechanisms differ among causes. Increasing the glutathione concentration and free radical concentration may be a common therapeutic mechanism to hearing loss from many insults, but these mechanisms are common to myriad disease states. D-methionine, for example, can bind to the platinum metal center of cisplatin, and as such, may displace protein-bound L-methionine from the platinum center. This binding property could be one mechanism through which D-methionine acts as an otoprotective agent for cisplatin administration. However, this mechanism cannot be one that is important for noise-induced ototoxicity as there is no specific toxic agent for D-methionine to interact with. Thus, the therapeutic mechanisms for noise-induced and cisplatin-induced hearing loss are different.

Furthermore, the effectiveness of similar compounds for a given insult differs greatly. For example, Jones et al. report that methionine and related compounds are the most effective agents against nephrotoxicity associated with CDDP administration as compared to a number of other agents tested, many of which are sulfur-containing nucleophiles.[12] In addition, unlike some other sulfur compounds and other amino acids, methionine can be reversibly oxidized and can act as a direct free radical scavenger. This oxidative behavior may be one property that makes methionine an advantageous anti-ototoxicity agent.

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[12]Jones, M.M; Basinger, M.A. *Anticancer Res.* **1989**, *9*, 1937.

CONCLUSION

Applicant submits that the present application is now in a condition for allowance and requests early allowance of the pending claims.

A check in the amount of $225.00 for a two month extension of time. The Commissioner is hereby authorized to charge any underpayment and credit any overpayment of government fees to Deposit Account No. 19-1345.

Respectfully submitted,

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